

(19) Europäisches Patentamt  
European Patent Office  
Office européen des brevets



(11) EP 0 727 232 A2

(12)

## EUROPEAN PATENT APPLICATION

(43) Date of publication:  
21.08.1996 Bulletin 1996/34

(51) Int Cl. 6: A61L 27/00, A61F 2/12

(21) Application number: 96300768.7

(22) Date of filing: 05.02.1996

(84) Designated Contracting States:  
BE DE ES FR GB IT NL SE

- Purkait, Bobby  
Montecito, California 93108 (US)
- Bhate, Anand  
Irving, Texas 75061 (US)
- Woo, Yi-Ren  
Flower Mound, Texas 75028 (US)

(30) Priority: 14.02.1995 US 389751

(71) Applicant: MENTOR CORPORATION  
Santa Barbara, CA 93111 (US)

(72) Inventors:

- Brunstedt, Michael  
Irving, Texas 75061 (US)

(74) Representative: Thomson, Paul Anthony  
Potts, Kerr & Co.  
15, Hamilton Square  
Birkenhead Merseyside L41 6BR (GB)

### (54) Filling material for soft tissue implant prostheses and implants made therewith

(57) A new soft tissue implant filling material is disclosed. The material may be polyvinylpyrrolidone, polyvinyl alcohol, hydroxypropylmethyl cellulose, polyethylene oxide, hyaluronic acid, sodium or calcium alginate,

hydrogel polyurethane, hydroxyethyl starch, polyglycolic acid, polyacrylamide, hydroxyethylmethacrylate (HEMA), and several naturally derived biopolymers including sodium kinate, seaweed, and agar.

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**Description****BACKGROUND OF THE INVENTION****1. FIELD OF THE INVENTION:**

The present invention is directed to the field of soft tissue implant prostheses, such as breast and testicular implants and tissue expanders, and more specifically, is directed to a filling material for such implants.

**2. ART BACKGROUND:**

Soft tissue medical implants generally are made of a silicone medical grade elastomer shell and a filling material disposed inside of the shell. If the shell ruptures, either as a result of accidents or through crease-fold flaw or failure, the filling material escapes into the body. For this reason, if the filling material is a gel it is desirable that the gel contain only biocompatible ingredients, have a low total solids content, be excretable or metabolizable and be sterile.

Soft tissue medical implants, such as breast implants, testicular prostheses, chin, cheek, pectoral and calf implants and the like, but particularly, breast implants, have gone through a tremendous transition over the past few years as a result of various concerns, justified or not, regarding the safety of silicone gel filling materials. As a result, a number of materials have been proposed to replace the silicone gel materials which have been commonly used over the past 30 years, or longer.

For example, in U.S. Patent No. 4,731,081 a number of materials including polyvinylpyrrolidone (PVP), polyvinyl alcohol, hydroxyethyl starch, lecithin, peanut oil, cottonseed oil, fatty acid salts and fatty acid esters have been proposed to prevent the problem of fold flaw.

U.S. Patent No. 4,772,284 relates to a breast implant filled with collagen gel or a gel made from poly-alpha amino homopolymers or random copolymers having a molecular weight in the range of 5,000 to 400,000.

U.S. Patent No. 4,787,905 relates to a gel for a breast prosthesis consisting of a mixture of hydroxyterminated polybutadiene resin, diundecylphthalate, polymethylenepolyphenyl isocyanate and dibutyltin dilaurate catalyst which cures to form a gel.

U.S. Patent No. 4,995,885 relates to an implant with alleged radiolucent characteristics made from biocompatible triglycerides, such as peanut oil or sunflower oil, having an effective atomic number of 5.9.

U.S. Patent No. 5,287,857 relates to an implant with a gel filling material of water and a cellulose gelling agent, such as carboxymethyl cellulose, methylcellulose, hydroxyethylcellulose, or the like. A lubricating agent additive is also proposed.

U.S. Patent No. 5,219,360 relates to a filling material for an implant comprising a gel made of cross-linked

hyaluronic acid and hyalan.

No one has heretofore proposed that alginate gel may be used as a filling material. There is a significant amount of research on alginate materials, which will be discussed briefly herein. In molecular terms, alginates constitute a family of unbranched polysaccharides of 1-4 linked  $\beta$ -D-mannuronic acid (M) and  $\alpha$ -L-guluronic acid (G), of composition and sequence dependent on the organism or tissue form which they are isolated. In seaweed alginates, such as that isolated from *Laminaria hyperborea*, the two monomers are arranged in a pattern of blocks along the chain, with homopolymeric regions (termed M and G blocks) interspersed with regions of alternating structure (MG blocks).

It is the G-blocks of alginates which impart one of its most useful and important properties, namely, the ability of alginic acid to form water insoluble salts by electrostatic interactions with some multivalent ions (e.g.,  $\text{Ca}^{2+}$ ,  $\text{Ba}^{2+}$ ,  $\text{Al}^{3+}$ ). Divalent cations, such as calcium, bind preferentially to G-blocks in a highly cooperative manner that has been termed the "egg-box model". Homogeneous alginate emulsions can be made using  $\text{CaCl}_2$  or other calcium salts in combination with ethanol, and phosphatidylcholine. Pronova Biopolymers, Inc. has recently begun promoting some highly purified alginates designed for certain biomedical applications. More specifically, the company produces ultra-pure grades with a very low content of protein, endotoxin, heavy metals and polyphenols. The company supplies alginates from *Laminaria hyperborea*, a seaweed naturally high in G content, which have been shown not to stimulate cytokine (e.g., IL-6,  $\text{TNF}-\alpha$ ) production when incubated with monocytes.

George Blaine, in 1944, is credited with first illustrating that calcium/sodium alginate is resorbable in animals. Histologically, resorption usually occurs by phagocytosis in the absence of a dense inflammatory capsule, necrosis, fibrosis or scar tissue formation. Alginates are listed as non-irritants to human skin and eyes in the most recent BIBRA Toxicology Report. Extensive testing has established that alginate is safe when used in a body.

Clinically, Oliver and Blaine, in 1949, used alginate as an absorbable hemostat in various types of brain surgery. Since the 1940's alginate has been used successfully in other deep surgeries, as an intravenous plasma expander, for intraperitoneal and subcutaneous injections of various drugs, in various surgeries of the eye, ear, nose, mouth, throat and sinuses, as a hemostat for ulcers of the gastrointestinal tract, in morphine rectal suppositories and medical examinations of the colon, rectum and vagina, as wound, burn and surgical dressings, for ileostomal impressions, and even to correct ingrown toe-nails.

None of these prior art patents recognize or address most of the important technological issues which are involved in the selection of an appropriately safe and effective implant filling material. It would be desirable to

provide a new filling material which is safe and effective and is an improvement over the characteristics of the prior art materials.

#### SUMMARY OF THE INVENTION

The present invention is a surgically implantable soft tissue implant filling material having a number of desired characteristics, many of which have not heretofore been recognized in the prior art.

The important characteristics are as follows:

- 1) The filling material should be compatible with the shell or membrane containing the filling material, as well as other components of the implant,
- 2) The viscosity, which is often a reflection of the molecular weight of the filling material and the solids content, should provide a soft tissue like feel to the implant and be maintained for the expected service life of the device,
- 3) The filling material should be sterile,
- 4) The osmolality of the filling material should be the same or similar to the osmolality of body fluids,
- 5) The pH of the filling material should be neutral or near neutrality,
- 6) The filling material may be buffered in order to maintain the pH within the desired range,
- 7) Antioxidants may be included to enhance long term stability of the material,
- 8) The filling material should be sufficiently lubricious to reduce the risk of abrasive failure of the implant,
- 9) The radiolucency of the filling material should be greater than that of silicone gels, and should be optimized, and
- 10) The filling material should be biocompatible; including non-toxic, and relatively easily excreted or metabolized in the body with no adverse effects.

Several materials have been identified which may meet these criteria. Those materials include polyvinylpyrrolidone (PVP), polyvinyl alcohol (PVA), hydroxypropylmethylcellulose and derivatives, polyethylene oxide (PEO), hyaluronic acid (HYA or HUA), sodium or calcium alginate, hydrogel polyurethane, hydroxyethyl starch (HES), polyglycolic acid, polyacrylamid, hydroxyethylmethacrylate (HEMA), and several naturally derived biopolymers including sodium kinate, seaweed and agar.

One gel formulation of the present invention, in its preferred embodiment consists of sodium alginate in the range of 0.25% to 15% and preferably, 1% to 5%, as a viscosifier,  $\text{CaCl}_2 \cdot 2\text{H}_2\text{O}$  in the range of 0.1% to 1.2% and preferably, 0.2% to 0.5% as an electrostatic gelling agent; 0.001% to 0.5%, and preferably 0.005% to 0.15%, phosphatidylcholine in 0.1% to 8% and preferably 0.5% to 5% ethanol as lubricity agent and antioxidant, respectively, and various salts for isotonic balancing. In addition, 0.03% to 0.13% and preferably 0.04% to 0.08% ceftazidime and 0.002% to 0.05% and preferably 0.004% to 0.012% miconazole may be added as antimicrobial and antifungal agents, respectively. Furthermore, sodium deoxycholate or other bile acids could be substituted as the lubricity agent. Glycerin, mannitol or other polyhydric alcohols, NaI, and  $\text{MgCl}_2$  could be substituted as the antioxidant.

One of the advantages of using an electrostatically cross-linked gel is that if the silicone implant shell should rupture, the calcium from the gel will be exchanged by excess sodium ions in the biological milieu converting calcium alginate to sodium alginate, which is soluble in body fluids and can be hydrolyzed by leukocytes or enzymes or be excreted via the spleen or the kidneys.

Another advantage of using electrostatic gellation of the G-blocks is that there are so many G-blocks within each chain that the normal process of hydrolysis may occur many times without compromising the three-dimensional network. Thus, these gels maintain their viscous properties longer than most synthetic or natural free polymer chains and longer than some covalently cross-linked synthetic or natural polymers.

Another gel formula in accordance with the present invention is based upon polyacrylamide and derivatives thereof. The solid content of such a formulation is in the range of 2 to 20%. The viscosity is in the range of 15,000 to 75,000 cps. The molecular weight range of the polyacrylamide is 200,000 to 1.5 million.

#### DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENT

The materials of the present invention have the following particularly advantageous characteristics:

1) Compatibility with the shell or membrane: The filling material must necessarily be compatible with the shell material in that it cannot react with the shell, and the shell must be capable of retaining the filling material without substantial leakage or bleeding. There shall be no degradation of shell or membrane physical properties and other components (e.g., valves, patches, washers) due to contact with filling material. The standard shell materials typically used in medical implants include polydimethyl siloxane, polyurethane, polyurethane/polyester copolymer, or other similar viscoelastic membranes. One test for bleed of the filling material through the

shell involves the solubility of the filling material in the shell material, or the measurement of the Hildebrand parameter, which is a measure of polymer-liquid interaction at the interface between the filler and the shell. For non-aqueous filling materials, the Hildebrand parameters of the filling material and the shell or membrane should be sufficiently different to discourage bleed. A high molecular weight of the filling material will also discourage bleed.

2) Viscosity and molecular weight: These parameters relate to the feel of the prosthesis, making the preferred filling material more gel-like than liquid-like. Additionally, it is necessary to provide both chemical and mechanical stability so that the filling material does not lose its soft tissue-like feel either during storage or in the body at body temperature. For the purposes of the present invention, an appropriate balance between viscosity and isotonicity, which is related to the molecular weight and the solids content, on the one hand, and biocompatibility of the material, which is a function of its excretability, ability to be metabolized, and its long-term toxicology effects, on the other hand, is important in the selection of an appropriate filling material.

3) Sterility: The material must be sterilizable by heat or radiation or chemical or filtration methodology, and should be compatible with appropriate antimicrobial additives. Several antimicrobial and antifungal agents which are shown to be effective include ceftazidime or other third generation cephalosporins, miconazole and amphotericin B.

4) Osmolality: The osmolality should be in the range of 200 to 400 mOsm/kg.

5) pH: The pH should be in the range of pH 6 to 8.

6) Buffering: An appropriate buffer may be added and should be compatible with the material to maintain the appropriate pH and stability of the filling material.

7) Antioxidants: Appropriate antioxidants, such as  $MgCl_2$ , may be added to enhance the stability of the formula.

8) Lubricity: Lubricity agents may be added to improve the ability of the filling material to protect the envelope from abrasion.

9) Radiolucency: The radiolucency of the filling material should be comparable with or better than that of 0.9% saline.

10) Biocompatibility: The material should be biocompatible. As used herein biocompatibility means

that the material is either excreted from the body, or is easily metabolized into harmless byproducts. Non-metabolized materials must be sufficiently small that they can be transported through membranes and excreted by the body in the urine or fecal matter. Overall, the material should not demonstrate any long-term adverse affect.

Several ideal compositions have been identified and their formulations are set forth below:

Alginate:

A calcium alginate gel is a presently desired form of the filling material, and is made by combining sodium alginate with calcium chloride or other calcium salts in an appropriate ratio. The composition consists of the following components:

20 Sodium alginate: 0.25% to 15% and preferably, 1 to 5%, and most preferably, 2%

25 Calcium chloride dihydrate ( $CaCl_2 \cdot 2H_2O$ ): 0.1% to 1.2%, and preferably 0.2% to 0.5%, and most preferably 0.32%.

PC (phosphatidylcholine): 0.001% to 0.5%, preferably 0.005% to 0.15%, and most preferably 0.01%.

30 Sodium Chloride: 0.2% to 0.5% to make the formulation isotonic.

Ethanol: 0.1% to 8%, preferably 0.5% to 5%.

35 The osmolality range for the final alginate gel is 200 mOsm/kg to 400 mOsm/kg, and preferably 250 mOsm/kg to 350 mOsm/kg.

The viscosity of the alginate gel is in the range of 5,000 cP to 150,000 cP, and preferably 50,000 cP to 40 120,000 cP as measured by a Brookfield model DV-II+ viscometer at and a shear rate of  $0.42sec^{-1}$ .

The pH of the final alginate gel is broadly in the range of 5 to 10, and preferably 6 to 8.

45 The alginate has a guluronic acid content above 30%. Also, bacterial alginate which has been modified with a mannuronic acid epimerase would fulfill the necessary characteristics of an appropriate alginate material.

50 In the presently preferred formulation, the calcium alginate gel is formed by mixing five solutions of low viscosity together:

1) Solution I:

55 A mixture of 13 volum % of (a) and 87 volum % of (b). Note: The solution will have a blue hue; but no precipitation occurs.

(a) 0.77 g of PC in 100 ml of EtOH;

(b) 0.9 wt%  $\text{CaCl}_2 \cdot 2\text{H}_2\text{O}$  in USP water for injection;

2) Solution II:

USP water for injection;

3) Solution III:

3.33 wt% sodium alginate and 1.0 wt% NaCl in USP water for injection;

4) of Solution IV:

USP water for injection;

5) Solution V:

1.1 wt%  $\text{CaCl}_2 \cdot 2\text{H}_2\text{O}$  in USP water for injection.

These solutions are preferably filtered through a  $0.2\mu$  filter and filled into mammarys in the following way (for every 100 ml of calcium alginate gel):

(1) Filter 11.5 ml of Solution I into each mammary using filter #1.

(2) Filter 5 ml of Solution II into each mammary using filter #1.

(3) With as little agitation as possible, filter 60 ml of Solution III into each mammary using filter #2. After each mammary is filled, mix the solution rather vigorously by massaging the mammary with hands for about 45 seconds.

(4) Filter 5 ml of Solution IV into each mammary using filter #1. Mix to form a homogeneous solution.

(5) Filter enough air into each mammary so that the contents of the mammary are well below the fill tube inlet opening.

(6) With as little agitation as possible, filter 2.0 ml of Solution V to each mammary 1 using filter #1 (see footnote 1). After each mammary is filled, mix the solution rather vigorously by massaging the mammary with hands until the solution becomes homogeneous. The solution should thicken quickly. Continue massaging each mammary for an additional 30 seconds.

The mammary prostheses are then packaged into double thermoforms with lids or pouches after the fill valve is sealed with a silicone adhesive. This package is shipped inside a zip-lock bag (to provide moisture barrier) for terminal sterilization. Electron beam irradiation,

<sup>1</sup> Mixture splashing back to the inlet will result in gel formation and blockage of the opening. If blockage should occur, try massaging the inlet opening area. Do not apply high pressure to a blocked inlet, since it may result in a separation of the fill tube component.

gamma irradiation or autoclave may be used to terminal sterilize the package after removing it from the zip-lock bag. The package is then be placed into a foil pouch and sealed up.

5 Phosphatidylcholine (PC) is a desired component of the gel. It provides several different functions. PC is amphiphilic, thus, it is a lubricity agent for the silicone rubber shell. PC also competes with the alginate chains for calcium cations, transforming a calcium alginate brittle gel into a flowing gel. This property is consistent with previous uses of PC as a gel dispersant and is believed to aid in excretion of large quantities of the gel should the shell rupture. PC acts as an emulsifier, which has been shown to increase both polysaccharide and cephalosporin stability. The compatibility of alginate with PC has been established in other systems such as microencapsulated liposomes, wound dressings and transdermal controlled release systems.

20 PC has been used clinically in parenteral preparations of doxorubicin, amphotericin, benzodiazepines, penicillin, and vitamins as well as an emulsifier for essential fatty acids and oils in total parenteral nutrition.

For the use of an alginate filling material in an inflatable prosthesis, it may be desirable to incorporate antimicrobial and antifungal agents. Although alginates are very resistant to bacteria when compared to other polysaccharides, some microorganisms do produce alginases. Bacterial and fungal growth studies were performed using the most commonly encountered bacteria and fungi in the operating rooms of hospitals. The study concluded that 0.06% ceftazidime and 0.008% miconazole produced a three (3) or more log reduction in the population of all the challenging organisms. Miconazole is a broad spectrum antifungal, that also has activity against gram-positive bacteria. In addition, the mentioned concentration of ceftazidime is higher than the minimal inhibitory concentration of all reported ceftazidime resistant strains; however, should simultaneous rupture of 2-800 cc implants occur, the amount of ceftazidime and miconazole released would be lower than a single prophylactic intravenous or intramuscular dose, and therefore, the amounts of antibiotics used in the present invention are believed to be safe.

The literature contains several citations involving 45 the use of intraluminal steroids, antimicrobials, antiinflammatories and pain relievers. To date, hundreds of thousands of patients have received hip or knee prostheses fixed with antibiotic containing cement. It has also become clinically routine to impregnate vascular grafts or catheter cuffs with antibiotics.

A polar steroid such as cortisol has a permeation 50 value for silicone rubber of  $0.00025 \mu\text{g mm}^{-1}\text{h}^{-1}$ . PC, miconazole and ceftazidime have been chosen with polar groups and molecular weights greater than steroids (330-450Da.), so that migration through the shell should be negligible.

All sterilization methods investigated, with the exception of filtration, cause depolymerization of alginate.

Using free radical scavengers can enhance the stability of the alginate solution to electron beam irradiation, gamma irradiation or autoclave. Testing showed that the gel with 6% glycerol or mannitol, or 0.5 to 5% ethanol maintained an acceptable viscosity after irradiation or autoclave.

Sodium Hyaluronate:

1. 1 to 10% hyaluronic acid with modified balanced salts (USP or NF grade): 0.075% KCl, 0.048%  $\text{CaCl}_2$ , 0.030%  $\text{MgCl}_2$ , and NaCl in sterile pyrogen-free water to achieve the osmolality range specified below. ( $\text{MgCl}_2$  also serves as an antioxidant agent.)
2. 0.03 to 0.13% Ceftazidime and 0.002 to 0.05% miconazole.
3. The viscosity of the hyaluronic acid gel is 5,000 - 150,000 cps at 37°C and the osmolality is 200 to 400, and preferably 250-350 mOsm/kg.

PVA

3A. 6% polyvinyl alcohol (PVA) (M.W. equivalent to Elvanol 52-22; 40 KD) with 0.07 ml of 25% glutaraldehyde (cross-linking agent), 0.3 ml 85%  $\text{H}_3\text{PO}_4$ , 4 ml 1.85 M NaOH per 100 ml of 6% PVA solution and 0.66% NaCl in sterile pyrogen-free water.  
or

3B. 3% PVA (M.W. equivalent to Elvanol 50-42; 75 KD) with 0.06 ml of 25% glutaraldehyde (cross-linking agent), 0.3 ml 85%  $\text{H}_3\text{PO}_4$ , 4 ml 1.85 M NaOH per 100 ml of 6% PVA solution and 0.66% NaCl in sterile pyrogen-free water.  
or

3C. 10% PVA (M.W. equivalent to Elvanol 52-22; 40 KD) and 0.66% NaCl in sterile pyrogen-free water buffered to pH 7 with 0.05M  $\text{NaH}_2\text{PO}_4$ .  
or

3D. 2 to 30% PVA synthesized from Ethanol based Solvent (MW range 10 - 50 KD) with similar combination of crosslinking agent, buffering and stability agents as previously discussed in 3A, 3B or 3C.

The molecular weight which provides an appropriate viscosity for PVA is preferably in the range of 10,000 to 40,000 Daltons.

HPMC

Hydroxypropyl methyl cellulose (HPMC) and its derivatives may be employed as filling materials in the present invention. Derivatives of HPMC include hydroxylalkyl cellulose, sodium carboxymethyl cellulose,

hydroxyethyl cellulose, hydroxypropyl cellulose, methylhydroxypropyl cellulose, methyl cellulose and ethylhydroxyethyl cellulose.

1 to 10% HPMC solid content of low to medium molecular weight (MW 10,000 to 40,000 Dalton). The viscosity can be enhanced with the addition of less than 1% p-benzoquinone. Similar antimicrobial and antifungal agents as those discussed in the above examples are used.

10

POLYACRYLAMIDE

15 Polyacrylamide, in a linear, branched chain, or cross-linked form can be used as a filling material in accordance with the present invention. As a preliminary matter, it has been found that commercially available material is not sufficiently pure, and therefore, purification is desired for the preferred embodiment.

20 PREPARATION AND PURIFICATION OF POLYACRYLAMIDE FOR USE IN VISCOELASTIC SOLUTIONS

25 Raw Materials

Acrylamide, Electrophoresis Grade or other commercially available

30  $\text{N}, \text{N}'\text{-methylenebisacrylamide}$

Triethanol amine (TEA)

Ammonium Persulfate

35 Ammonium Sulfate

Deionized Water (DI water), 12  $\text{M}\Omega$  or better

40 Ethanol, USP

45 Polymerization

The polymerization is carried out in solution. The concentration is selected so that the resulting polymer solution is stirrable.

45 Acrylamide (and methylenebisacrylamide, or other crosslinking agent, if used) and ammonium sulfate are dissolved in DI water in a polymerization vessel. While stirring, the solution is charged with nitrogen and the vessel continuously purged with nitrogen to eliminate and exclude oxygen from the reaction. Ammonium persulfate and TEA are dissolved in DI water in separate containers and the solutions charged with nitrogen. The reaction is initiated by adding the ammonium persulfate solution followed by the TEA solution without admitting oxygen to the reactor. The reaction may be run adiabatically or the temperature controlled by a heating or cooling bath. The polymerization is run essentially to com-

pletion, which typically requires several hours.

#### Precipitation

The polymer is separated from the solution by precipitation with alcohol. Any lower alcohol may be used, but preferably ethanol is used. The precipitation may be carried out in the polymerization reactor, or the polymer solution transferred to a suitable vessel.

While stirring the solution, alcohol is added slowly until the polymer becomes insoluble and precipitates from solution. This occurs rapidly over a very narrow range of alcohol concentration. More alcohol is added to bring the slurry volume to about four times the initial solution volume and stirring continued for a period of time to allow the polymer particles to equilibrate with the alcohol water solution and firm up. The solid polymer is then collected on a filter. The polymer particles are then reslurried in alcohol and stirred for a period of time. The collection and reslurring is repeated. At this point, the polymer has previously been dried, but it would be more efficient to hold it as a slurry in alcohol.

#### Purification

Most of the salts and unreacted monomer remained in the aqueous phase on precipitation of the polymer. The residual monomer is reduced to an acceptable level by extraction with water-alcohol solution.

Dry polymer powder or polymer filtered from alcohol-water slurry is placed into a beaker or other suitable vessel and slurried in alcohol water solution. The alcohol concentration is adjusted so that the polymer particles will be swollen, but will not agglomerate. After a period of time, the alcohol concentration is increased to firm up the particles for separation from the liquid on a filter. This process is repeated for four extraction cycles. The polymer particles are then slurried in an alcohol-water solution with the alcohol concentration adjusted so as to produce a desirable residual alcohol content in the dried polymer. The polymer is collected on a filter and dried.

#### Drying

The mass of wet polymer is spread on glass trays and vacuum dried without heat. This typically requires two days. For larger volumes, a vacuum tumble dryer would be effective.

It will be understood by person of ordinary skill in the art that many changes, additions, deletions and substitutions can be made to the present invention, the presently preferred embodiment of which is described herein, without departing from the spirit and scope of the present invention.

#### Claims

##### 1. An implantable soft tissue prosthesis comprising:

5 a hollow shell formed of a flexible elastomeric envelope, said shell having an inner volume and an exterior surface, said prosthesis being adapted to be surgically implanted and to retain a desired shape when filled with a filling material;  
 10 said filling material comprising a gel or viscous liquid that is selected from the group consisting of polyvinylpyrrolidone, polyvinyl alcohol, hydroxypropylmethyl cellulose, polyethylene oxide, hyaluronic acid, sodium or calcium alginate, hydrogel polyurethane, hydroxyethyl starch, polyglycolic acid, polyacrylamide, hydroxyethylmethacrylate (HEMA), and several naturally derived biopolymers including sodium kinate, seaweed, and agar, wherein said filling material has an osmolality in the range of 200 to 400 mOsm/kg, and a radiation penetration comparable with or better than that of 0.9% saline.

25 2. The implant of claim 1 wherein the pH of said filling material is in the range of 6 to 8.

30 3. The implant of claim 1 further comprising an appropriate buffer.

35 4. The implant of claim 1 further comprising antimicrobial and antifungal agents and combinations thereof.

5. The implant of claim 4 wherein said antimicrobial and antifungal agents are selected from the group consisting of miconazole, ceftazidime or other third generation cephalosporin and amphotericin B.

40 6. The implant of claim 1, wherein the filling material comprises:

45 a) 0.25 % to 15 % by weight sodium alginate;

b) 0.1 to 1.2%  $\text{CaCl}_2 \cdot 2\text{H}_2\text{O}$

c) 0.001 % to 0.5 % phosphatidylcholine and

50 d) wherein the viscosity of the formulation gel is in the range of 5,000 cp to 150,000 cp at 37°C and a shear rate of 0.42 sec<sup>-1</sup>.

7. The implant of claim 6 wherein the osmolality is 200 to 400 mOsm/kg.

55 8. The implant of claim 6 wherein the alginate is from *Laminaria hyperborea*.

9. The implant of claim 6 wherein the alginate is bacterial alginate which has been modified with an epimerase. 5

10. The implant of claim 6 wherein the alginate has a guluronic acid content above 30%. 10

11. The implant of claim 1 wherein the filling material comprises: 15

a) 1 to 10% hyaluronic acid with modified balanced salts, 0.075% KCl, 0.048%  $\text{CaCl}_2$ , 0.030%  $\text{MgCl}_2$ , and NaCl in sterile pyrogen-free water;

b) 0.03 to 0.13% ceftazidime and 0.002 to 0.05% miconazole;

c) and wherein the viscosity of the HNA gel is 5,000 to 150,000 cps at 37°C and the osmolality is 200 - 400 mOsm/kg. 20

12. The implant of claim 1 wherein the filling material comprises: 25

a) 0.002 to 0.05 % miconazole;

b) 0.03 to 0.13% ceftazidime;

c) polyvinyl alcohol selected from the group consisting of: 30

i) 6% polyvinyl alcohol, 0.07 ml of 25% glutaraldehyde, 0.3 ml 85%  $\text{H}_3\text{PO}_4$ , 4 ml 1.85 M NaOH per 100 ml of 6% polyvinyl alcohol solution and 0.66% NaCl; 35

ii) 3% polyvinyl alcohol, 0.06 ml of 25% glutaraldehyde, 0.3 ml 85%  $\text{H}_3\text{PO}_4$ , 4 ml 1.85 M NaOH per 100 ml of 6% polyvinyl alcohol solution and 0.66% NaCl; 40

iii) 10% polyvinyl alcohol and 0.66% NaCl buffered to pH 7 with 0.05M  $\text{NaH}_2\text{PO}_4$ ; and 45

iv) 2 to 30 % PVA (MW range 10 - 50 KD) with glutaraldehyde,  $\text{H}_3\text{PO}_4$ , NaOH and 0.66% NaCl.

13. An implantable soft tissue prosthesis comprising: 50

a hollow shell formed of a flexible elastomeric envelope, said shell having an inner volume and an exterior surface, said prosthesis being adapted to be surgically implanted and to retain a desired shape when filled with a filling material; 55

said filling material comprising a gel or viscous liquid that is selected from the group consisting of 1 to 10 % hydroxypropylmethyl cellulose (HPMC) and its derivatives, said derivatives being selected from the group consisting of hydroxyalkyl cellulose, sodium carboxymethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, methylhydroxypropyl cellulose, methyl cellulose and ethylhydroxyethyl cellulose, said HPMC having a molecular weight in the range of 10,000 to 40,000, wherein said filling material has an osmolality in the range of 200 to 400 mOsm/kg, and a radiation penetration comparable with or better than that of 0.9% saline.

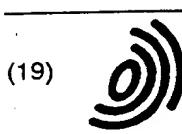
14. The implant of claim 1 wherein the filling material comprises polyacrylamide and/or derivatives thereof having a solid content of such a formulation in the range of 2 to 20%, a viscosity in the range of 15,000 to 75,000 cps and a molecular weight range of the polyacrylamide in the range of 200,000 to 1.5 million.

15. The implant of claim 1 further comprising a low molecular weight alcohol.

16. The implant of claim 1 wherein the low molecular weight alcohol is ethanol.

17. The implant of claim 1 further comprising an antioxidant.

18. The implant of claim 1 further comprising a lubricity agent.



(19) Europäisches Patentamt

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## EUROPEAN PATENT APPLICATION

(88) Date of publication A3:  
06.11.1996 Bulletin 1996/45

(51) Int Cl. 6: A61L 27/00, A61F 2/12

(43) Date of publication A2:  
21.08.1996 Bulletin 1996/34

(21) Application number: 96300768.7

(22) Date of filing: 05.02.1996

(84) Designated Contracting States:  
BE DE ES FR GB IT NL SE

• Purkait, Bobby

Montecito, California 93108 (US)

• Bhate, Anand

Irving, Texas 75061 (US)

• Woo, Yi-Ren

Flower Mound, Texas 75028 (US)

(30) Priority: 14.02.1995 US 389751

(74) Representative: Thomson, Paul Anthony

Potts, Kerr & Co.

15, Hamilton Square

Birkenhead Merseyside L41 6BR (GB)

(71) Applicant: MENTOR CORPORATION  
Santa Barbara, CA 93111 (US)

(72) Inventors:

• Brunstedt, Michael  
Irving, Texas 75061 (US)

### (54) Filling material for soft tissue implant prostheses and implants made therewith

(57) A new soft tissue implant filling material is disclosed. The material may be polyvinylpyrrolidone, polyvinyl alcohol, hydroxypropylmethyl cellulose, polyethylene oxide, hyaluronic acid, sodium or calcium alginate,

hydrogel polyurethane, hydroxyethyl starch, polyglycolic acid, polyacrylamide, hydroxyethylmethacrylate (HEMA), and several naturally derived biopolymers including sodium kinate, seaweed, and agar.



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## EUROPEAN SEARCH REPORT

Application Number  
EP 96 30 0768

| DOCUMENTS CONSIDERED TO BE RELEVANT  |   |  |   |                 |                                  |          |           |                  |             |
|--|---|--|---|-----------------|----------------------------------|----------|-----------|------------------|-------------|
| Category   | Citation of document with indication, where appropriate, of relevant passages   | Relevant to claim  | CLASSIFICATION OF THE APPLICATION (Int.Cl.) |                 |                                  |          |           |                  |             |
| X  | WO-A-93 22987 (CYTRX CORP) 25 November 1993<br>* page 18, line 35 *<br>* page 19, line 1 - line 13; claims *<br>---   | 1  | A61L27/00<br>A61F2/12                       |                 |                                  |          |           |                  |             |
| X  | WO-A-94 07434 (LIPOMATRIX INC) 14 April 1994<br>* claims *<br>---   | 1  |   |                 |                                  |          |           |                  |             |
| X  | EP-A-0 186 430 (AMERICAN MED SYST) 2 July 1986<br>* claims *<br>---   | 1  |   |                 |                                  |          |           |                  |             |
| X  | US-A-4 731 081 (TIFFANY JOHN S ET AL) 15 March 1988<br>* claims *<br>---  | 1  |   |                 |                                  |          |           |                  |             |
| X  | PLASTIC AND RECONSTRUCTIVE SURGERY, vol. 91, no. 6, May 1993, pages 1057-1062, XP000572165<br>NEAL HANDEL ET AL.: "AN IN VIVO STUDY OF THE EFFECT OF VARIOUS BREAST IMPLANT FILLER MATERIALS ON MAMMOGRAPHY"<br>* page 1059 * | 1  |   |                 |                                  |          |           |                  |             |
| X  | FR-A-2 693 901 (LATOUCHE XAVIER) 28 January 1994<br>* the whole document *<br>---   | 1  |   |                 |                                  |          |           |                  |             |
| X  | WO-A-93 00867 (CHRISTENSEN JAMES MARLOW ;AINPOUR PARVIZ ROBERT (US)) 21 January 1993<br>* claims; examples 1-7 *<br>---   | 1  |   |                 |                                  |          |           |                  |             |
| A  | EP-A-0 338 813 (KOKEN KK ;SHISEIDO CO LTD (JP)) 25 October 1989<br>* claims; examples *<br>---  | 1  |   |                 |                                  |          |           |                  |             |
|  |   | -/-  |   |                 |                                  |          |           |                  |             |
| <p>The present search report has been drawn up for all claims</p> <table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 33%;">Place of search</td> <td style="width: 33%;">Date of completion of the search</td> <td style="width: 34%;">Examiner</td> </tr> <tr> <td>THE HAGUE</td> <td>6 September 1996</td> <td>ESPINOSA, M</td> </tr> </table> |   |  |   | Place of search | Date of completion of the search | Examiner | THE HAGUE | 6 September 1996 | ESPINOSA, M |
| Place of search  | Date of completion of the search  | Examiner   |   |                 |                                  |          |           |                  |             |
| THE HAGUE  | 6 September 1996  | ESPINOSA, M  |   |                 |                                  |          |           |                  |             |
| CATEGORY OF CITED DOCUMENTS  |   | T : theory or principle underlying the invention<br>E : earlier patent document, but published on, or after the filing date<br>D : document cited in the application<br>L : document cited for other reasons<br>& : member of the same patent family, corresponding document |   |                 |                                  |          |           |                  |             |
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### CLAIMS INCURRING FEES

The present European patent application comprised at the time of filing more than ten claims.

- All claims fees have been paid within the prescribed time limit. The present European search report has been drawn up for all claims.
- Only part of the claims fees have been paid within the prescribed time limit. The present European search report has been drawn up for the first ten claims and for those claims for which claims fees have been paid,  
namely claims:
- No claims fees have been paid within the prescribed time limit. The present European search report has been drawn up for the first ten claims.

### LACK OF UNITY OF INVENTION

The Search Division considers that the present European patent application does not comply with the requirement of unity of invention and relates to several inventions or groups of inventions,  
namely:

See sheet -B-



All further search fees have been paid within the fixed time limit. The present European search report has been drawn up for all claims.



Only part of the further search fees have been paid within the fixed time limit. The present European search report has been drawn up for those parts of the European patent application which relate to the inventions in respect of which search fees have been paid.

namely claims:



None of the further search fees has been paid within the fixed time limit. The present European search report has been drawn up for those parts of the European patent application which relate to the invention first mentioned in the claims.

namely claims:



## EUROPEAN SEARCH REPORT

Application Number  
EP 96 30 0768

| DOCUMENTS CONSIDERED TO BE RELEVANT  |  |                   |   |                 |                                  |          |           |                  |             |                                    |  |  |   |  |  |  |  |  |
|--|--|-------------------|---|-----------------|----------------------------------|----------|-----------|------------------|-------------|------------------------------------|--|--|---|--|--|--|--|--|
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| X  | FR-A-2 568 127 (GEISTLICH SOEHNE AG) 31 January 1986<br>* claims *   | 1,14              |   |                 |                                  |          |           |                  |             |                                    |  |  |   |  |  |  |  |  |
| X  | PLASTIC AND RECONSTRUCTIVE SURGERY, vol. 94, no. 2, 1 August 1994, pages 306-317, XP000572178<br>KANT LIN ET AL: "HYALURONIC ACID-FILLED MAMMARY IMPLANTS: AN EXPERIMENTAL STUDY"<br>* page 307 - page 309 * | 1,11              |   |                 |                                  |          |           |                  |             |                                    |  |  |   |  |  |  |  |  |
| X  | WO-A-93 20780 (UNIV PENNSYLVANIA ;PHILADELPHIA CHILDREN HOSPITAL (US)) 28 October 1993<br>* claims *   | 1,11              |   |                 |                                  |          |           |                  |             |                                    |  |  |   |  |  |  |  |  |
| X  | US-A-5 219 360 (GEORGIADE NICHOLAS G) 15 June 1993<br>* claims *   | 1,11              |   |                 |                                  |          |           |                  |             |                                    |  |  |   |  |  |  |  |  |
| X  | WO-A-94 25078 (SEBBIN LAB ;LE PESTEUR JACQUES (FR); CHITARRINI GINO U (FR)) 10 November 1994<br>* claims *   | 1,11              | TECHNICAL FIELDS<br>SEARCHED (Int.Cl.)      |                 |                                  |          |           |                  |             |                                    |  |  |   |  |  |  |  |  |
| X  | FR-A-2 677 539 (MAS JEAN CLAUDE) 18 December 1992<br>* claims *  | 1                 |   |                 |                                  |          |           |                  |             |                                    |  |  |   |  |  |  |  |  |
| X  | US-A-5 344 451 (DAYTON MICHAEL P) 6 September 1994<br>* column 4, line 26 - line 68; claims *  | 1,11,13           |   |                 |                                  |          |           |                  |             |                                    |  |  |   |  |  |  |  |  |
| X  | FR-A-2 691 068 (ARION HENRI) 19 November 1993<br>* the whole document *  | 1,13              |   |                 |                                  |          |           |                  |             |                                    |  |  |   |  |  |  |  |  |
|  |  | -/-               |   |                 |                                  |          |           |                  |             |                                    |  |  |   |  |  |  |  |  |
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## LACK OF UNITY OF INVENTION

The Search Division considers that the present European patent application does not comply with the requirement of unity of invention and relates to several inventions or groups of inventions, namely:

1. Claims 1 (partially); 2-5,15-18 (completely) :  
An implantable soft tissue prosthesis comprising a hollow shell and a filling material comprising a gel or viscous liquid consisting of polyvinylpyrrolidon.
2. Claims 1(partially); 6-11 ,13 (completely) :  
An implantable soft tissue prosthesis comprising a hollow shell and a filling material comprising a gel or viscous liquid consisting of hydroxypropylmethyl cellulose, hyaluronic acid, sodium or calcium alginate, hydroxyethyl starch and several naturally derived biopolymers including sodium kinate, seaweed and agar.
3. Claims 1 (partially); 12 (completely) :  
An implantable soft tissue prosthesis comprising a hollow shell and a filling material comprising a gel or viscous liquid consisting of polyvinyl alcohol.
4. Claims 1 (partially); 14 (completely) :  
An implantable soft tissue prosthesis comprising a hollow shell and a filling material comprising a gel or viscous liquid consisting of polyacrylamide.
5. Claim 1 (partially) :  
An implantable soft tissue prosthesis comprising a hollow shell and a filling material comprising a gel or viscous liquid consisting of polyethylene oxide.
6. Claim 1 (partially) :  
An implantable soft tissue prosthesis comprising a hollow shell and a filling material comprising a gel or viscous liquid consisting of hydrogel polyurethane.
7. Claim 1 (partially) :  
An implantable soft tissue prosthesis comprising a hollow shell and a filling material comprising a gel or viscous liquid consisting of hydroxyethyl methacrylate (HEMA).



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## EUROPEAN SEARCH REPORT

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| X  | FR-A-2 707 499 (NAVATEL PATRICE) 20 January 1995<br>* claims *                      | 1,13              |   |                 |                                  |          |           |                  |             |
| X  | EP-A-0 575 035 (PERRY LARRY ;MAXWELL PATRICK G (US)) 22 December 1993<br>* claims * | 1,13              |   |                 |                                  |          |           |                  |             |
|  |   |                   | TECHNICAL FIELDS SEARCHED (Int.Cl.)         |                 |                                  |          |           |                  |             |
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